Influence of anesthetic technique on survival after tumor debulking surgery of elderly patients with ovarian cancer: Results of a retrospective cohort study

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Abstract. Epidural analgesia could influence the postoperative oncologic outcomes in patients with specific types of non-metastatic solid neoplasms. The present study aimed to investigate the impact of anesthetic technique on survival in elderly patients with ovarian cancer (OC). The records of all women with OC older than 60 years of age undergoing tumor debulking surgery at the University Medical Center of the Johannes Gutenberg University Mainz (Mainz, Germany) between January 2008 and December 2019 were obtained. The study cohort was divided into two groups based on the use of perioperative epidural anesthesia or not. First, Kaplan-Meier analysis was performed to analyze the prognostic influence of anesthetic technique on survival. Second, multivariate Cox proportional hazards model was adjusted for multiple conventional prognostic factors concerning three main categories: i) Current clinical-pathological tumor characteristics; ii) anesthesiologic parameters, including mean age, American Society of Anesthesiologists Performance Status and preexisting comorbidities summarized in the Charlson Comorbidity Index; and iii) oncological and surgical parameters such as oncological radicality and Surgical complexity Score. A total of 110 patients were included in the study and 71 (64.5%) of them received epidural analgesia. The median survival time was 26.0 months from primary debulking surgery and no significant differences in progression-free (PFS) and overall survival (OS) were noted between the 'Epidural' and 'non-Epidural' cohorts. After adjustment for the selected risk factors from the three categories, the effects of epidural analgesia on PFS and OS remained non-significant [PFS: hazard ratio (HR), 1.26; 95% CI, 0.66-2.39; and OS: HR, 0.79; 95% CI, 0.45-1.40]. The present results did not support the independent association between epidural-supplemented anesthesia and improved PFS or OS in elderly patients with standardized ovarian cancer debulking surgery.

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Introduction

Ovarian carcinoma (OC) is one of the most common neoplasms of the female reproductive tract (1). With over 240,000 new diagnoses and 152,000 annual deaths worldwide in 2020 according to the Global Cancer Statistics (2), OC exhibits the worst prognosis among gynecological malignancies (3). With a median age of 68 years at diagnosis, OC is a typical cancer of the older generation (4). However, increasing biological age is independently associated with more aggressive and advanced diseases (5,6).

At present, radical primary or interval surgical debulking remains as the preferred first-line treatment option, possibly with extensive multivisceral cytoreduction to achieve complete macroscopic tumor reduction with no residual tumor burden (7-9). Although, excessive surgical resections have been shown to initiate metastasis via circulating tumor cells to blood and lymph or activate dormant pre-existing micrometastases (10-12). Whether the minimal residual tumor burden results in clinical metastases depends primarily on the balance between the body's immunity and natural killer (NK) cell activity and the tumor's ability to proliferate or colonize a new site (13). The most popular hypothesis about the immunomodulation effect of surgical stress explains the adverse impact of the inhibition of the body's innate tumor defense mechanism (14). Otherwise, an effective immune response is affected by the integrated network of different cytokines, including interleukins and interferons. Certain cytokines are antitumorigenic and permit cancer growth (e.g. IL-2 and IFN-γ), whereas others are pro-tumorigenic and promote the immune system's anti-tumor capability (e.g. IL-6 and IL-8) (15).

Interestingly, the technique of anesthesia may influence the long-term outcome of solid cancer patients by modulating the neuroendocrine and cytokine imparted immune competence and stress response during excessive surgery (16,17). Compared with general anesthesia using intravenous opioids or inhaled anesthetics, regional anesthesia can effectively increase the level of activated NK cells to preserve host immunity, as a primary immunological defense against cancer cells (18,19). This possible survival advantage for epidural-supplemented anesthesia with decreased levels of opioids depends on a reduction of cancer recurrences and postoperative mortality without metastasis, mainly in elderly cancer patients (20,21). Besides, exposure to volatile anesthetics leads to resistance of cancer cells against apoptosis in a dose-dependent pattern (22). Moreover, opioids may suppress the NK cell cytotoxicity, as one component of the human cellular immune system, as well as promote tumor growth by activating the μ-opioid receptor (23,24). As an unavoidable adverse effect of general anesthesia during partial cell vagotomy, an endocrine stress response followed (25).

Thereof, this study aimed to evaluate the prognostic influence of epidural-supplemented anesthesia on cancer survival in a highly specified cohort of older ovarian cancer patients after major oncological surgery.

Materials and methods

Inclusion and exclusion criteria. Patients with all stages of OC [based on the 2010 FIGO staging system (26)] older than 60 years of age, who underwent standardized surgical treatment at the University Medical Center of the Johannes Gutenberg University Mainz between January 2008 and December 2019, were included in the retrospective cohort study. Standardized oncological surgery required primary or interval tumor debulking operations to decrease the postoperative residual tumor burden as much as possible (aim R0 resection) and was defined as a further inclusion criterion. Exclusion criteria were: 1) surgically treatment not in the University Medical Center Mainz, 2) Non-malignant or borderline ovarian tumors, 3) No information about epidural analgesia available and 4) No complete follow-up information. Long-term follow-up was performed by evaluation of patient's clinical records, written inquiries to the patients or their physicians, and by telephone calls up to February 2021. The follow-up ended at death, and the longest follow-up period lasted nearly 11.5 years (June 2008-December 2019 according to 138 months).

Baseline characteristics. We screened the archives and the electronically patients' records to gather all using general patient information. Clinical-pathological tumor characteristics were collected according to the current national guidelines, which may influence the postoperative prognosis in OC patients. These factors are summarized within three categories: 1) *clinical-pathological tumor parameters*, including the tumor stage [TNM and International Fédération of Gynecology and Obstetrics (FIGO) (26)], histological subtype and grading, 2) *anesthesiologic parameters* such as comorbidities [summarized in the Charlson Comorbidity Index (CCI) (27,28)] and American Society of Anesthesiologists Performance Status (ASA PS) (29) and 3) *oncological and surgical parameters* (e.g. postoperative residual tumor burden, surgical radicality retrospectively evaluated through Surgical Complexity Score (SCS) (30), as well as timing and completeness of chemotherapy).

Anesthetic techniques. Epidural catheter anesthesia was placed during the anesthesiologic induction before the surgical intervention. Epidural analgesia was administrated in OC patients expect those with contraindications like local infections or malformations, as well as spinal surgery or trauma, bacteremia, that may cause epidural infection and urinary tract infections, for example. Furthermore, low coagulation status or insufficient stopping time anticoagulant and patients who refused the technique were absolute contraindications for epidural anesthesia. Relative contraindications arise from preexisting neurological deficits and failures such as signs of paralysis subsequently slipped disc. Intraoperative epidural anesthesia was provided by bupivacaine 0,25% or ropivacaine 0,375% with or without addition of epidural sufentanil according to the attending anesthetist. All patients that received epidural catheter placement were treated by postoperative patient-controlled epidural anesthesia consisting of bupivacaine 0.125%. Epidural fentanyl was added as long as the patients were in intensive or intermediate care units, whereas bupivacaine 0,125% alone was applied in the normal ward. Patients that did not receive epidural catheter placement or showed signs of insufficient epidural anesthesia received a patient-controlled intravenous anesthesia-device with piritramide. All patients were cared for by a physician-based acute pain service affiliated to the Department of Anesthesiology as long as they received a patient-controlled anesthesia.

General anesthesia was conducted as balanced or total intravenous anesthesia according to the standard operating procedures of the Department of Anesthesiology as amended (31,32).

Statistical analysis. The data were recorded in Microsoft Excel and SPSS statistical software program, version 23.0 V5 R (SPSS Inc, Chicago, IL, U.S.A.), as well as StataBE 17 V5 were performed for the data analyses. Patients' characteristics were expressed as a mean +/- standard deviation [SD], or as median with their interquartile range [IQR]. We divided the study cohort into two groups, according to the epidural supplementing. Normal distribution was explored by Shapiro-Wilk test. Categorical variables were compared using the chi-square or Fisher's exact test. Kaplan-Meier estimates were used to determine the progression-free survival (PFS) and overall survival (OS) rates after five years for univariate analyses. The Log-Rank-Test was used to compare the curves. Timepoints in months were the date of diagnosis which resulted in the date of tumor debulking surgery up to death (or recurrence) or last follow-up. PFS included loco-regional lower abdomen recurrences and/or distant metastasis and death as an event. The Cox proportional hazards regression model was determined for multivariate analyses of the survival time after debulking surgery. At first, univariate Cox regression analyses for all factors that affect oncological survival after cancer surgery were performed. Secondly, each hypothesis with a significance level of <0.05 was included in the multivariate Cox regression analysis. The variable selection was examined via backward

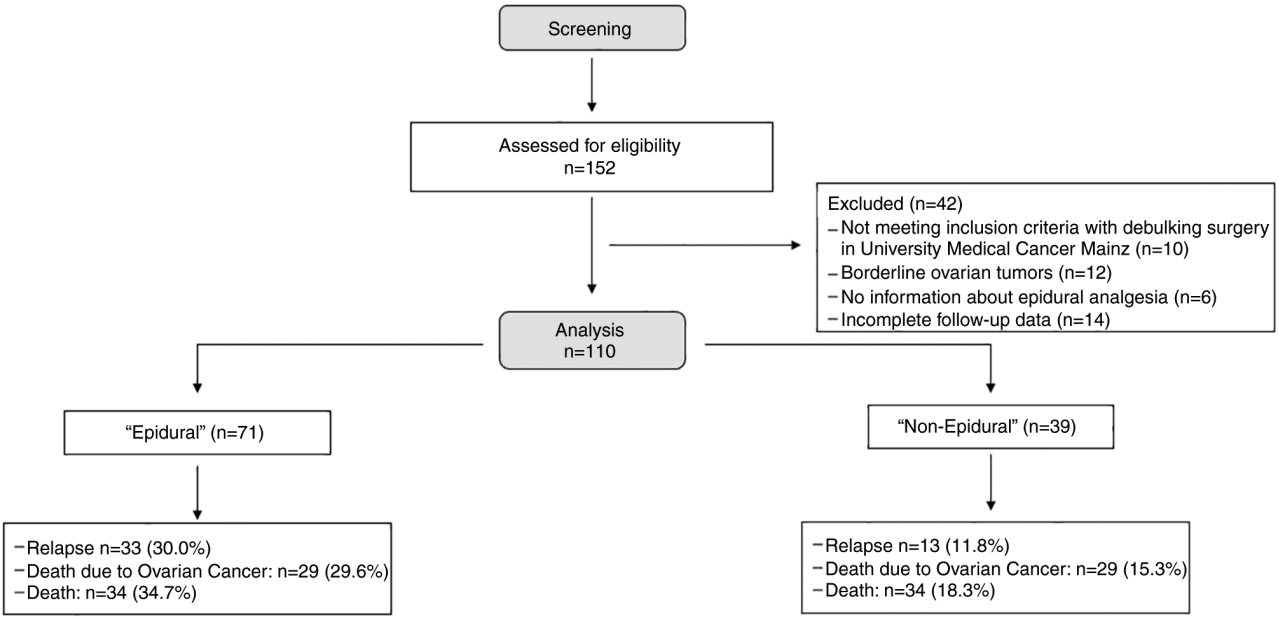

Figure 1. Consort Statement. n, number of analyzed women.

elimination. All tests were two-sided and a P-value of <0.05 was considered statistically significant. Because no correction was made for multiple testing due to the exploratory nature of the study, these are descriptive measures that should be interpreted with caution.

Results

Clinical features of OC patients. A total of 152 patients, with OC were screened and recruited from the achieves of the University Medical center Mainz (Fig. 1). Our final cohort was composed of 110 women aged 60 years and older (mean 70.9+/-5.9 years). Missing data arise from the inclusion and exclusion criteria (Fig. 1). All baseline factors, including various clinical-pathological tumor characteristics, as well as anesthesiologic, oncological and surgical parameters, were compared between the 'Epidural' and 'non-Epidural' group. Demographic and clinical characteristics are summarized in Table I.

Comparison of baseline clinical data between the two groups. Most patients were diagnosed with high-grade serous histology (n=77, 70.0%) and had a higher histological grading (G3: n=82, 75.9%). Approximately fifty-eight percent of the patients (n=63) underwent optimal tumor debulking. We reported no differences between the 'Epidural' and the 'non-Epidural' group concerning the clinical prognostic parameters (all P values >0.05) with the expectation of the ASA PS and CCI evaluation (P=0.020) (Table I). Furthermore, a lower number of relevant comorbidities was associated with more epidural-supplemented anesthesia. The median survival time for all OC patients was 26.0 months (11.8-38.0). The 'Non-Epidural' cohort survived with 27.0 months (15.0-39.0) longer than the 'Epidural'-supplemented group with 19.0 months (8.0-36.5), respectively. No significant differences were found between the groups (P=0.355).

Comparison of survival data between the two groups. The Kaplan-Meier analyses indicated no association between epidural-supplemented anesthesia and prolonged progression-free or overall survival (PFS: 32.8% vs. 27.8%; P=0.478 and OS: 29.5% vs. 15.0%; P=0.409; respectively) (Fig. 2). In contrast, the preoperative ASA classification showed statistically significant differences in terms of 5-years OS (ASA 2 49.9% vs. ASA 3 12.9%; P=0.023) as also shown in Fig. 3. In the subgroup of ASA 2 patients, significantly more patients received combined anesthesia with epidural anesthesia as solely general anesthesia (77.1% vs. 22.9%; P=0.020) whereby no differences were found in the ASA 3 group ('Epidural': 55.7% vs. 'non-Epidural': 44.3%).

The Cox regression model indicated no significant association between epidural use and prolonged survival after cancer debulking surgery (PFS: HR: 1.26; 95%-CI [0.66-2.39] and OS: HR: 0.79; 95%-CI [0.45-1.40]; respectively) (Table II). In the multivariate Cox model, only the conventional clinical-pathological tumor parameter TNM-tumor stage retained its independent significance for PFS and OS (PFS: HR: 3.09; 95%-CI: [1.72-5.55] and OS: HR: 3.11; 95%-CI: [1.73-5.58]; respectively).

Discussion

The results of this retrospective study did not confirm a definite association between epidural-supplemented anesthesia and cancer progression and OS in elderly patients following tumor debulking surgery for all stages of ovarian cancer.

Possible benefits of regional anesthesia techniques on the postoperative analgetic effect in gynecological malignancies, especially in OC patients have been examined (33,34). With regard to survival data of OC related to the presence of an epidural, controversial data have been published (35-39). Overall, the positive impact of neuraxial analgesia seems to be solely detectable in more advanced disease, the prolonged

Table I. Patient characteristics for the two types of anesthesia techniques.

Parameter	Total (n=110)	Epidural (n=71)	Non-epidural (n=39)	P-value
Clinical-pathological tumor characteristics				
Tumor stage (TNM), n (%) (n=107)				0.272
I	17 (15.9)	10 (9.3)	7 (6.5)	
II	8 (7.5)	7 (6.5)	1 (0.9)	
III	81 (75.7)	52 (48.6)	29 (27.1)	
IV	0 (0.0)	0 (0.0)	0 (0.0)	
Tx	1 (0.9)	0 (0.0)	1 (0.9)	
Tumor stage (FIGO), n (%) (n=106)				0.106
Early ovarian cancer < FIGO IIa	15 (14.2)	7 (6.6)	8 (7.5)	
Late ovarian cancer ≥ FIGO IIa	91 (85.8)	62 (58.5)	29 (27.4)	
Histological subtype, n (%) (n=110)				0.240
Low grade serous + others	33 (30.0)	24 (21.8)	9 (8.2)	
High grade serous	77 (70.0)	47 (42.7)	30 (27.3)	
Histological grading, n (%) (n=108)				0.854
G1	6 (5.6)	4 (3.7)	2 (1.9)	
G2	20 (18.5)	14 (13.0)	6 (5.6)	
G3	82 (75.9)	52 (48.1)	30 (27.8)	
Anesthesiologic characteristics				
Mean age, years (+/-SD)	71.08 (+/-5.95)	72.18 (+/-6.17)	70.55 (+/-5.75)	
CCI, n (%) (n=110)				0.020
CCI 1	22 (20.0)	18 (16.4)	4 (3.6)	
CCI 2	61 (55.5)	41 (37.3)	20 (18.2)	
CCI 3	27 (24.5)	12 (10.9)	15 (13.6)	
American Society of Anesthesiologists				
Performance Status, n (%) (n=109)				0.020
1+4	0 (0.0)	0 (0.0)	0 (0.0)	
2	48 (44.0)	37 (33.9)	11 (10.1)	
3	61 (56.0)	34 (31.2)	27 (24.8)	
Oncological and surgical characteristics				
Postoperative residual tumor burden, n (%) (n=109)				0.533
None	63 (57.8)	42 (38.5)	21 (19.3)	
Present	46 (42.2)	28 (25.7)	18 (16.5)	
SCS, n (%) (n=110)				0.837
SCS 1	37 (33.6)	23 (20.9)	14 (12.7)	
SCS 2	53 (48.2)	34 (30.9)	19 (17.3)	
SCS 3	20 (18.2)	14 (12.7)	6 (5.5)	
Completeness of chemotherapy, n (%)	75 (68.2)	62 (82.7)	13 (17.3)	0.008
Timing of chemotherapy, n (%) (n=99)				0.911
Neoadjuvant chemotherapy	22 (22.2)	14 (14.1)	8 (8.1)	
Adjuvant chemotherapy	77 (77.8)	50 (50.5)	27 (27.3)	
Clinical events, n (%)				
Relapse	46 (41.8)	33 (30.0)	13 (11.8)	0.181
Death due to OC	44 (44.9)	29 (29.6)	15 (15.3)	0.937
Death	52 (53.1)	34 (34.7)	18 (18.3)	0.834

Comparison of baseline clinical data between the two groups. To compare the categorical variables, a χ^2 test was used. OC, ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; CCI, Charlson Comorbitidy Index; SCS, Surgical Complexity Score.

relapse-free survival seems to depend on the timing of catheter insertion. In the study by Tseng *et al* (35), 435 women with advanced stages of OC receiving epidural anesthesia during primary debulking surgery were compared to

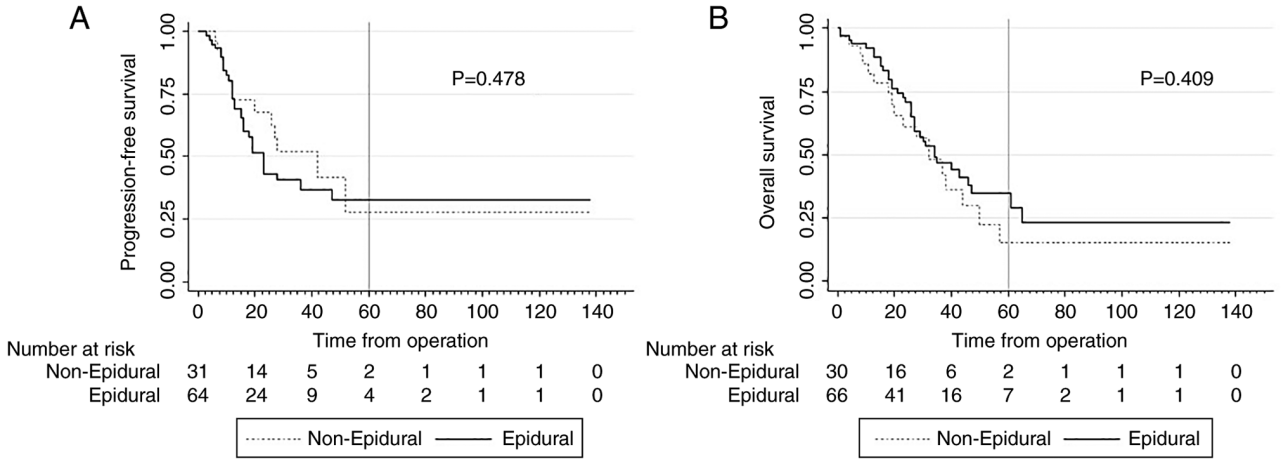

Figure 2. Kaplan Meier survival estimates in association with the use of an epidural analgesia. (A) Progression-free survival: Epidural vs. non-epidural. (B) Overall survival: Epidural vs. non-epidural.

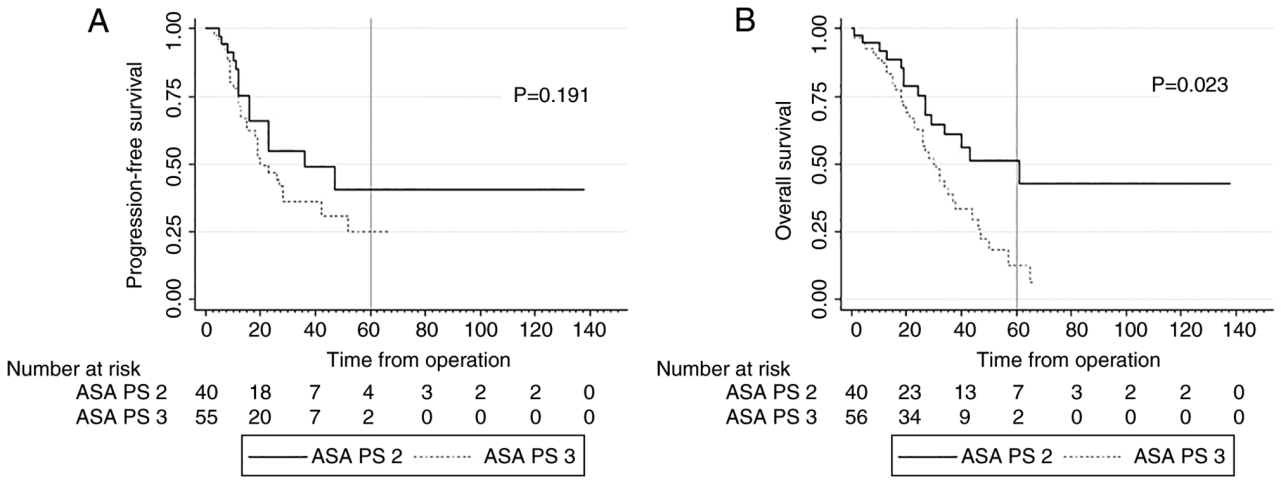

Figure 3. Kaplan Meier survival estimates in association with ASA PS classification. (A) Progression-free survival: ASA PS2 vs. ASA PS3. (B) Overall survival: ASA PS 2 vs. ASA PS 3. ASA PS, American Society of Anesthesiologists Performance Status.

213 patients did not. The median PFS and OS was significantly improved in those who received epidurals (PFS: 20.8 months vs. 13.9 months; P=0.021 and OS: 62.4 months vs. 41.9 months, P<0.001; respectively). Oliveira and colleagues demonstrated the epidural-related preservation of the immune system function resulting in an increased time to tumor recurrence after surgery in 182 patients executively for intraoperative used epidural catheters (HR: 0.37; 95%-CI [0.19-0.73]) (37).

Other published reports showed similar findings to those of the current study. In Lacassies's prospective clinical registry, there were no benefits in survival in patients with advanced stages of OC after the use of epidural reported (38). They obtained propensity score matching, adjusting for chemotherapy, besides the multivariate Cox regression model, without any differences in cancer prognosis. In 2012, Capmas *et al* (39) examined 104 advanced-stage OC patients and declared no clear impact of regional analgesia on cancer recurrence. A systematic Cochrane Review addressing this topic showed no association between epidural use with lengthened survival in solid cancer patients (40).

Physiologic negative stress was highest at the time of surgery and affected the adaptive immune surveillance (41). Immune disturbance due to surgical distress may facilitate cancer cell migration (16). Various types of anesthesia showed different effects on human cancer immunity and carcinogenesis. Epidural analgesia could attenuate intraoperative suppression of NK cell function and help preserve effective defense against tumor progression, by limiting the use of opioids (42). Additionally, regional anesthesia was linked to earlier recovery times by reducing postoperative complications such as thromboembolic, cardiac and pulmonary, as well as gastrointestinal complications and inflammation (43). The role of cytokines in cancer immunity was either directly influenced by proliferative effects or indirectly by enhancing proinflammatory and proangiogenic pathways in host cells.

The results of our trial suggested that survival prognosis in OC disease might not be primarily determined by immunomodulatory effects caused by the epidural analgesia, especially not in elderly cancer patients. Although, increasing age resulted in changes in body's homeostasis and

Table II. Cox univariate and multivariate regression analyses.

	Univariate analysis						Multivariate analysis					
	PFS			OS			PFS			OS		
Parameter	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Clinical-pathological tumor parameters												
Tumor stage-TNM	2.81	1.59-4.95	<0.001	3.70	2.05-6.68	<0.001	3.09	1.72-5.55	<0.001	3.11	1.73-5.58	<0.001
Tumor stage-FIGO	6.78	2.07-22.26	0.002	11.47	2.73-47.91	0.001	2.14	0.38-12.21	0.392	2.13	0.37-12.17	0.394
Histological subtype	1.48	0.77-2.87	0.241	1.73	0.90-3.29	0.098[a]	-			-		
Histological grading	1.68	0.94-3.02	0.082[a]	1.78	1.01-3.14	0.048	-			1.14	0.63-2.08	0.667
Anaesthesiologic parameters												
Mean age	0.79	0.44-1.42	0.428	1.19	0.69-2.06	0.533	-			-		
CCI	0.95	0.63-1.43	0.791	1.43	0.95-2.15	0.091[a]	-			-		
ASA PS	1.49	0.81-2.73	0.202	1.97	1.08-3.57	0.026	-			1.24	0.67-2.29	0.494
Epidural analgesia	1.26	0.66-2.39	0.487	0.79	0.45-1.40	0.413	-			-		
Oncological and surgical parameters												
Postoperative residual tumor burden	2.26	1.25-4.07	0.007	2.63	1.49-4.62	0.001	1.14	0.61-2.12	0.680	1.13	0.60-2.12	0.715
SCS	1.39	0.91-2.13	0.129	1.44	0.96-2.16	0.079[a]	-			-		
Completeness of CTX	1.76	0.69-4.48	0.234	0.65	0.30-1.40	0.267	-			-		
Timing of CTX	0.92	0.42-1.98	0.825	0.93	0.43-2.02	0.863				-		

[a]Survival data were analyzed using univariate and multivariate Cox regression analyses for all relevant baseline characteristics according to the technique of analgesia. PFS, Progression-free survival; OS, Overall survival; HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; CCI, Charlson Comorbidity Index; ASA PS, American Society of Anesthesiologists Performance Status; SCS, Surgical Complexity Score; CTX, chemotherapy.

vulnerability to external stressors increased the relevant prognostic factors remain. In advanced cancer diseases the best option of controlling progression and lengthening survival was optimal surgical tumor debulking as well as completeness of platinum-based chemotherapy (44). Anesthesia and analgesia techniques were important, but they did not appear to have an independent and significant impact on cancer prognosis in this population.

Study limitations arise from the biases associated with the retrospective single-institution nature of the study. The single institution design allowed the patients in both groups, 'Epidural' and 'non-Epidural' to receive the same perioperative care. Our follow-up period of almost 14 years was robust and we also performed a through multivariate analysis, controlling for conventional-established prognostic factors in OC. Even though, the intraoperative epidural technique was approximately homogenous (bupivacaine 0.25% or ropivacaine 0.375% and postoperative with bupivacaine 0.125% in combination with fentanyl concentration varied between 0.75% and 1.0% and was administered with or without an opioid).

Because of the fact that elderly patients were underrepresented in the vast majority of existing comparative reports, prospective studies to investigate the effects of perioperative epidural anesthesia use in the special cohort of elderly ovarian cancer women on survival are warranted. Given the limited number of modifiable prognostic parameters for elderly OC patients, studies investigating the impact of different anesthetic techniques potentially influencing the immune function after debulking surgery will be desirable.

In conclusion, we could not find a survival benefit in patients with ovarian cancer after the perioperative use of epidural anesthesia after debulking surgery. Primary tumor stage in combination with optimal cytoreduction and completeness of chemotherapy are still the strongest prognostic factors.

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Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KA and MJB contributed to the study design. KA, MJB, MWS, RS, AD, MS, SK, MR, RH, EKH and AH contributed to the data acquisition. KA and MJB analyzed the data. KA and MJB wrote the paper. KA and MJB confirm the authenticity of all the raw data. KA and MJB revised the manuscript for important intellectual content. All authors critically and substantively revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The retrospective cohort study was conducted in accordance with the 'Ethical principles for medical research involving human subjects' of the current version of the Declaration of Helsinki. Data collected for the present study were obtained as part of routine medical care. Ethical approval for use of these samples for research purposes was not required for the present study in accordance with local/national guidelines. Written informed consent from participants was obtained in accordance with local/national guidelines.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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